Seltzer's criticisms. The questions raised by (129) Seltzer have not been adequately answered by the 1968 document. The article is reproduced in its complete form.

An Evaluation of the Effect of Smoking on Coronary Heart Disease

I. Epidemiological Evidence

Carl C. Seltzer, PhD

In January 1964, the Surgeon General's Advisory Committee on Smoking and Health[1] in considering the available information on smoking and coronary heart disease (CHD) (International Statistical Classification [ISC] 420) reported that "male cigarette smokers have a higher death rate from coronary artery disease than nonsmoking males, but it is not clear that the association has casual significance."

Three points should be noted. First, the committee left no doubt that there was a consistent statistically significant association among cigarette smokers of increased mortality and morbidity from CHD in men, particularly during middle life. Seven large completed or current prospective studies of smoking and death rate gave a CHD median mortality ratio (current cigarette smokers to nonsmokers) of 1.7, with no significant excess deaths among cigar and pipe smokers. Second, the committee recognized that certain factors other than smoking were known or thought to predispose to the condition or to be also associated with an increased incidence. Included among these were age, sex, morphological constitution, heredity, occupations involving responsibility and stress, low levels of physical activity, diets high in saturated fats, high blood pressure, high serum cholesterol levels, and excessive obesity. Third, the point was made that if it could be shown that cigarette smokers and nonsmokers had significant constitutional differences apart from any differences that might be caused by smoking itself, then the possibility would exist that some predisposition of smokers to the disease might also be of constitutional origin and not caused by smoking. After reviewing some of this evidence, the committee concluded, "In spite of some bits of suggestive evidence the existence of basic constitutional differences between smokers and nonsmokers is not presently established."

The Surgeon General, Luther Terry, MD, on Jan 29, 1964, speaking of CHD stated, ". . . the committee was unable to reach a firm conclusion as to the role smoking plays in causing or precipitating a death from this disease. We need to find out for sure whether smoking is a factor in this disease or whether it should be exonerated . . . we have no real clues as to what it is in tobacco that influences coronary artery disease, if indeed it does."[2]

Since publication of the Surgeon General's Report on Smoking and Health in early 1964, there have appeared many statements with regard to the

See also pages 139 and 201.

relationship of cigarette smoking and CHD which go far beyond the limited conclusions of the Surgeon General's Advisory Committee and the then Surgeon General. Some of these statements come from US Public Health officials, from responsible persons in medicine and science, and from numerous medical societies throughout the country, as well as many other sources. For example, in 1965 it was stated, "Ultimate elimination of cigarette smoking . . . would mean the saving of some 250,000 Americans from premature deaths caused by or associated with cigarette smoking . . . half of these premature deaths associated with cigarette smoking are due to cardiovascular diseases, particularly

From the Department of Nutrition, Harvard University School of Public Health, Boston.

Reprint requests to 665 Huntington Ave, Boston 02115.

10050659

Source: https://www.industrydocuments.ucsf.edu/docs/ntlk0000

coronary artery disease. . . ."[1][2][3] In 1965, it was affirmed that ". . . the association [American Heart Association] believes that there is a total of approximately 250,000 excess premature deaths associated with cigarette smoking each year in the United States, and that of those, about 125,000 are associated with cardiovascular disease, principally coronary heart disease. . . . We have excellent evidence that heavy cigarette smoking, a pack or more a day, particularly accelerates atherosclerosis, and accentuates its effects, makes it worse. This accounts for the increased premature deaths that are associated with cigarette smoking so far as coronary artery disease is concerned."[1][2][3] In 1966 it was said, "In view of the mountain of evidence now available this is no longer a 'controversial' matter. The massive evidence indicating that cigarette smoking is a major coronary risk factor in middle-aged Americans and British men have been reviewed in many places . . ."[4] Again in 1966, it was declared ". . . unforgiveable for us to write off the 48 million adults in the United States who are now cigarette smokers. After all, these are the people in whom the extra hundreds of thousands of premature deaths will be occurring each year for the next 20 or 30 years; these are the people who suffer from . . . the 300,000 extra coronaries . . ."[5]

From the statements, ". . . it is not clear that the association has causal significance" and ". . . the committee was unable to reach a firm conclusion as to the role smoking plays in causing or precipitating death from this disease . . ." of the Surgeon General and his Advisory Committee on Smoking and Health in January 1964, we have since been presented with "131,000 excess deaths," "125,000 excess premature deaths," "300,000 extra coronaries" each year that are "caused by" or "associated with cigarette smoking."

Attention should be focused on the phrases "caused by" and "associated with cigarette smoking." These phrases clearly imply that the consequences of smoking cigarettes is a variable amount of excess premature CHD deaths. But no such implication can be drawn from the conclusion of the Surgeon General's committee of 1964. The latter reported a higher death rate from CHD *among male cigarette smokers* than among nonsmokers. If one were to transcribe this statement in terms of "excess deaths," then it could be stated that there was an excess of CHD deaths *among cigarette smokers* than among nonsmokers. To shift from excess deaths *among* cigarette smokers to excess deaths *associated with cigarette smoking* is to attribute *causality* to cigarette smoking, an attribution which the advisory committee was unable to reach.

We have no reason for assuming that what we are dealing with here is a matter of semantics. Rather, the more likely event is that these statements causally linking mortality from CHD among cigarette smokers must represent conclusions reached by some from new evidence available since the issuance of the advisory committee report in 1964. It becomes important, then, to inquire into the nature of this new evidence. At the same time, it is necessary to inquire into the availability of additional new evidence bearing upon the question of genetic and constitutional factors between smokers and nonsmokers, particularly insofar as they are related to the etiology of coronary heart disease.

Some readers may object to the use of the phrase "caused by," since the words "cause and effect" are extremely difficult to define clearly. In using these words, we are following the practice of the Surgeon General's 1964 report, which attempted to explain (pp 20-21) the meaning which that committee attached to the term causality. In stating "cigarette smoking is causally related to lung cancer in men," the Surgeon General's committee implied that cigarette smoking increases the probability that lung cancer will develop in a man. With regard to cardiovascular disease, the committee stated, "it is not clear that the association has causal significance," implying that the evidence available to them was insufficient to judge whether cigarette smoking is an effective agent in increasing the probability of death from cardiovascular disease or not.

Purpose of the Report

The purpose of this report, then, is to review the more important publications dealing with smoking and CHD which have appeared subsequent to the Surgeon General's Report on Smoking and Health in 1964, to answer the following question:

What is the nature of the additional evidence on smoking and CHD which has resulted in the magnification and extension of the claims of the effects of cigarette smoking on mortality and morbidity from CHD?

This particular communication (part 1) will consider the epidemiological evidence only and is limited to data on men. Subsequent reports covering experimental and clinical data, and constitutional and genetic evidence are planned.

This analysis of the epidemiological evidence was submitted for publication almost simultaneously with the appearance of *The Health Consequences of Smoking*, a Public Health Service review published in late 1967.[6] Accordingly, this is an independent analysis and does not contain references to or comparisons with the 1967 report.

The Material

In the 3½ years since publication of the Surgeon General's report of 1964, a certain amount of epidemiological research has been completed or continued in this country or abroad. For the purpose of this report, consideration has been given to the more pertinent studies as follows: Doll and Hill study of British doctors,[7] the combined Albany and Framingham study,[8] Dorn's US veterans study,[9] Hammond's prospective study,[10] the Canadian veterans study,[11] the Evans County, Georgia study,[12] the Tecumseh, Michigan prospective

1005050660

Source: https://www.industrydocuments.ucsf.edu/docs/ntlk0000

study,[4] Reid and co-workers' migrant study,[5] the health insurance plan (HIP) studies,[6,7] and the national health survey.[8]

These investigations are not always comparable, since their study designs lead to incidence rates of disease manifestations in some and to prevalence rates of disease or illness disability in others. Incidence rates of mortality or morbidity derived from longitudinal prospective or retrospective studies may be quite a different matter than prevalence rates of disease, illness, or disability derived from cross-sectional studies of whatever nature. These distinctions are important and must be kept in mind in assessing the respective findings in these studies, especially in connection with mortality ratios computed from different base lines. The first four studies listed above are prospective studies of mortality or morbidity with attendant death rates or incidence rates of disease manifestations in large populations, and hence have certain elements of comparability. On the other hand, for example, the national health survey is a prevalence study and does not identify the rate at which various types of morbidity develop in differential groups in the population but simply reports the recent existence of illness or disability, or both. As such, its findings under certain conditions may be spurious and at best are supportive in nature when they identify relationships previously established in incidence studies.

(It is to be noted, however, that "surprisingly good agreement" between prevalence and incidence results was found by the Framingham heart study with respect to relative risks for CHD.)[9]

While all of these investigations deserve detailed individual analyses of their findings, the limitations of space do not permit such elaboration. Many important discrepancies or inconsistencies (as well as consistencies) in various aspects of these studies are overlooked when the results of the studies are characterized solely by their main conclusions. A topical analysis of important aspects of the studies affords a productive approach to an understanding of the relative consistency of the results of the investigations.

Epidemiological Data Published Since Surgeon General's Report of 1964

The more important new evidence relative to mortality and morbidity from CHD is summarized according to the following subject categories: (1) overall mortality and morbidity in smokers and nonsmokers, (2) morbidity from angina pectoris, (3) mode of tobacco smoking, (4) age of smokers, (5) amount of cigarette smoking, (6) duration of cigarette smoking, (7) inhalation, and (8) disease rates in ex-smokers in relation to the duration of the cessation of smoking.

Overall Mortality and Morbidity in Smokers and Nonsmokers.—The Surgeon General's 1964 report concluded that male cigarette smokers have a higher death rate from CHD than men who did not smoke. All the new evidence gives the same results, a *confirmation* of the earlier findings. This is not surprising, since the conclusions of the 1964 report were based on "seven large completed or current prospective smoking and death rate studies." Additional new prospective studies or the extension of observations on previously reported current studies on the same or similar populations would not be expected to give different results. Similarly, all the new evidence on morbidity, with the exception of the Tecumseh study of Epstein et al,[10] confirms the existence of higher CHD prevalence rates among smokers than among nonsmokers. It is not clear why the Tecumseh study CHD prevalence rates are higher in nonsmokers than in smokers at every age level up to 70 years.

The new evidence does not change the basic nature of the association of higher CHD death rates in cigarette smokers. It simply confirms the previous evidence. The new data, either through longer observation periods of follow-up of ongoing studies or through additional studies of large populations, in the main merely serve to provide an opportunity for a more precise look at various interrelationships. Furthermore, there has been no change in the intensity of the association, such as would be suggested if the new data showed consistently higher average CHD death rates for smokers compared to nonsmokers than did the older data. But this has not been the case. The Surgeon General's 1964 report indicated a median mortality ratio of 1.7 among persons currently smoking cigarettes. It is seldom noted, however, that the Doll and Hill study of British doctors' (one of the key mortality studies) showed a 33% greater mortality rate for cigarette smokers from "CHD without hypertension" than nonsmokers, a figure far below that of most other prospective studies. But in the main, the average value of the mortality ratio in the new studies is approximately that found in the older evidence.

Angina Pectoris.—The Surgeon General's 1964 report makes brief mention of the fact that "angina pectoris . . . is less closely associated with cigarette smoking than is myocardial infarction." Available new mortality data support the conclusion that cigarette smokers have higher death rates associated with myocardial infarction than nonsmokers. But the new data appear to be ambivalent with respect to angina pectoris.

The combined Albany and Framingham study[11] clearly shows no significant increase in incidence of angina among cigarette smokers compared with nonsmokers. It was even found that the morbidity ratio (Framingham series) for those who smoked 20 or more cigarettes per day (78) was below that of the non-cigarette smokers (86). The conclusion arrived at was that "The risk of angina pectoris as the sole or initial manifestation of CHD appears to be unrelated to the tobacco habit." On the other hand, both the HIP[7] and Reid and co-workers' migrant[5] studies gave opposite results. The HIP

1005050961

Source: https://www.industrydocuments.ucsf.edu/docs/ntlk0000

study (based on incidence) reported a statistically significant association between cigarette smoking and angina pectoris among men. The authors of this study, however, caution that, "variations in methodology and diagnostic criteria may explain this departure from other studies' observation of no difference in risk for angina among cigarette smokers and nonsmokers." The migrant study, based on prevalence of angina-like symptoms, is in agreement with the results of the HIP study. It is quite probable that Epstein et al's Tecumseh study[13] also provides evidence of an absence of association between smoking and angina pectoris, since their data showed a slightly lower prevalence of CHD (angina pectoris or electrocardiographic signs of myocardial disease) in smokers.

It should be pointed out, in further reference to angina pectoris, that Cederlof et al,[14] in a study of morbidity among monozygotic twins from Sweden, found a similar frequency of angina pectoris among smokers and nonsmokers, a finding in general agreement with the data of the combined Albany and Framingham study.

Uncomplicated angina pectoris comprises about 20% of all manifestations of CHD in men; elimination of such cases would mean elimination of a significant segment of CHD cases from consideration of being related to the tobacco habit.

Mode of Tobacco Smoking.—The Surgeon General's 1964 report pointed out that ". . . the association of coronary disease with the use of tobacco in other forms [apart from cigarettes] has not been striking." All the new evidence with regard to pipe and cigar smokers showed little or no increase in their death rates from CHD over that of nonsmokers. In the case of the Doll and Hill study of British doctors,[8] pipe or cigar smokers gave a lower death rate than the group of nonsmokers. In the Dorn study of US veterans,[11] the mortality ratios of persons who smoked cigars or a pipe were virtually the same as that of nonsmokers. The Hammond study of American men[15] showed pipe smokers on the whole had lower CHD death rates than nonsmokers, while the cigar smokers tended to have slightly higher rates than the nonsmokers.

Overall, it may be said that the new evidence appears to establish a lack of association of excess deaths due to coronary heart disease among pipe or cigar smokers, a less qualified finding than given in the 1964 report. CHD disability, on the other hand, may show slightly higher frequency in pipe or cigar smokers than nonsmokers.

The fact that there appears to be no evidence for excess CHD death risk among pipe or cigar smokers is a matter of considerable importance. This result from epidemiological surveys is a disquieting finding to those engaged in the study of the effects of tobacco smoking on health. For the most part, the problem has been simply ignored, perhaps in the hope that somehow or other it would just disappear by itself. But the discordance of an excess mortality due to CHD in cigarette smokers but not in cigar or pipe smokers cannot be summarily swept under the rug.

Nicotine in the tobacco smoke is regarded by many as the agent responsible for the effects on coronary heart disease. However, this discordance in disease effects is inexplicable in terms of amount of nicotine and other constituents of tobacco smoke. The 1964 report stated, "Calculations indicate that the nicotine absorbed (40 to 60 mg) from six cigars equals that from 30 cigarettes inhaled." The Doll and Hill study of British doctors showed no significant differences among cigarette smokers between the CHD death rates of inhalers and noninhalers.[8] We know very little about the possible mechanisms which might explain why cigarette smokers have greater CHD death rates than nonsmokers while pipe and cigar smokers do not.

At the present stage of our knowledge, this anomaly is inexplicable. It is clearly a subject for further research. For now, we can only conclude that this discrepancy between the mortality rates of cigarette smokers vs those of cigar or pipe smokers is difficult to reconcile with the concept that tobacco smoking is causally related to excess deaths due to CHD.

Age of Smokers.—Virtually all the new studies confirm the finding of the 1964 report that death rates from coronary heart disease are relatively higher in male cigarette smokers compared to nonsmokers in middle age than in old age. In general, cigarette smokers more than 65 years of age have lower CHD mortality ratios and disabilities than those less than 65 years of age. This may, in part, reflect a selective survival effect in smokers and/or a diminishing risk for CHD among cigarette smokers relative to other influencing factors with advancing age.

It is possible that the relatively greater CHD mortality ratio among younger smokers is more a function of the differential age changes in CHD death rates of nonsmokers than of smokers. The point can be illustrated by comparing the CHD death rates according to age of smokers and nonsmokers with those of the general US population. In the US population in 1964, the death rate due to CHD of men ages 55 to 64 was 2.6 times greater than that of men ages 45 to 54, 2.2 times greater in ages 65 to 74 than in ages 55 to 64, and 1.9 times greater in ages 75 to 84 than in ages 65 to 74.[11] In comparison, Dorn's data[11] on veterans currently smoking cigarettes showed CHD death rate for men ages 55 to 64 to be 2.5 times greater than that of men ages 45 to 54, 1.9 times greater for ages 65 to 74 than ages 55 to 64, and 1.6 times greater in ages 75 to 84 than in ages 65 to 74. Further, in nonsmokers ("never smoked or occasionally only") from Dorn's study of veterans, CHD death rate for ages 55 to 64 was 10.0 times greater than that of ages 45 to 54, 2.0 times greater in ages 65 to 74 than in ages 55 to 64, and 2.2 times greater in ages 75 to 84 than in ages 65 to 74.

From these data, it would appear that the successive decade age increases in CHD death rates of

10050662

Source: https://www.industrydocuments.ucsf.edu/docs/ntlk0000

the smokers parallel those of the US general population much more closely than do rates of the nonsmokers, with the nonsmokers particularly diverging from the general population in a far greater increase in CHD death rate from ages 45 to 54 to ages 55 to 64. Furthermore, in Dorn's study of veterans, the death rates for smokers are somewhat lower than those of the general public, and the death rates of persons who do not smoke are still lower. While it is difficult to make direct comparisons of death rates from one population to another, is it possible that the nonsmokers represent a very special and markedly singular group in the population, more so than the smokers?

Amount of Cigarette Smoking.—The Surgeon General's 1964 report states, ". . . the ratio of smokers' coronary death rates to those of nonsmokers increases progressively with the daily cigarette consumption." This increase in CHD death rates with increased amount of smoking was found in a number of studies.

However, an examination of the new data since the 1964 report reveals a very complex and hardly consistent picture. To begin with, a consistent positive gradient of CHD mortality with amount of cigarettes smoked is found only in the Dorn study,[11] Reid and co-workers' migrant study[14] (in British and Norwegian born but not in native born US men), and in white men of high social class in the Evans County, Georgia study.[15] "There is certainly no clear gradient [of CHD mortality] with number of cigarettes smoked" is the report by Doll and Hill in their survey of British doctors (a rising gradient is apparent in younger but not in older men), and no clear gradient is found in the Canadian veterans study,[13] and in the Negro and white men of low social class of the Evans County, Georgia study.[15]

Significantly, the majority of the new studies show inversions or inconsistencies in the gradient of mortality or morbidity with average number of cigarettes smoked daily. While it is true that in virtually all these instances, those who smoked the most cigarettes give consistently higher CHD and myocardial infarction rates than those who smoked the least, the consistency of the gradient is broken down as between the groups which smoked the least and the intermediate groups, with the intermediate rates the same or lower than the rates of the groups which smoked the least. Inversions between the groups which smoked the least (usually less than a pack a day) and the intermediate groups (at least one pack but less than two packs daily) are to be found in the combined Albany and Framingham study,[17] the Hammond study,[12] Reid and co-workers' migrant study (native born subjects),[14] the HIP investigation,[18] and the national health survey.[19]

Accordingly, it cannot be said that the new data confirm the results of the 1964 report with respect to a consistent rising gradient of CHD mortality with increased amounts of cigarettes smoked. On the contrary, the new data, with its many inconsistencies and inversions in the "rising gradient," indicate that this whole subject is not as clear cut as it appeared at first blush.

Parenthetically, it is to be noted that almost identical inversions in body build measurements according to amount of cigarettes smoked have been described by Seltzer in his study of morphological constitution and smoking habits of Harvard college graduates.[20]

Duration of Cigarette Smoking.—The 1964 report made no comment with regard to duration of smoking and CHD rates. Since the 1964 report, there have been three important studies which have dealt with this subject. The combined Albany and Framingham study[17] found an absence of association between duration of heavy cigarette smoking and risk of myocardial infarction. In Dorn's US veterans study there was also no significant relationship between duration of cigarette smoking and risk of death from CHD; Kahn summarized this by stating that there was ". . . an almost perfect fit of the data with a hypothesis of no relationship to duration."[11] And in the Canadian veterans survey there was no clear gradient of increasing CHD mortality with increasing years of smoking experience.[13] In fact, in this material, the mortality ratios for heart and circulatory diseases for those who had smoked cigarettes for 30 to 39 years (1.5) were lower than those of individuals who had smoked for a period of only 5 to 9 or 10 to 14 years (1.7 and 1.8, respectively).

It is notable that while duration of cigarette smoking is considered an important factor in connection with lung cancer mortality, the new evidence since the 1964 report points to an exoneration of this important element with respect to CHD. The evidence would appear to be consistent with the conclusion of the authors of the combined Albany and Framingham study that it is ". . . not any cumulative effect of inhaling cigarette smoke which precipitates myocardial infarction and death from CHD. . . ."[16]

This has led to the suggestion by the Framingham heart study that coronary heart disease is only *acutely* connected with cigarette smoking not *chronically* connected, acting by the "triggering of a lethal arrhythmia or thrombosis in subjects predisposed by an already compromised coronary circulation."[17] If this is indeed true, then the effect of smoking (by their suggestion) would be limited solely to those persons with "already compromised circulations." Does this signify that cigarette smoking is without deleterious effect on those with a normal, healthy coronary apparatus?

Inhalation.—The Surgeon General's 1964 report states, ". . . at each level of consumption the ratio (mortality ratio) increases with amount of inhalation reported by the smokers."

On this subject the new data give conflicting results. In the Doll and Hill study of British doctors,[13] the authors stated, "Only small and statis-

10050963

Source: https://www.industrydocuments.ucsf.edu/docs/ntlk0000

tically insignificant differences were observed in coronary disease without hypertension (3% excess in inhalers). . . ." Furthermore, the death rate for noninhalers (5.09) was substantially higher than that for nonsmokers (3.29). We should not lose sight of this latter point. If more extended observations of British doctors beyond the present ten years' observations tend to confirm this finding, this would make it appear that something else apart from the inhalation of cigarette smoke is responsible for the higher death rate from CHD of smokers over nonsmokers. In this regard, other known risk factors and constitutional differences between smokers and nonsmokers would have to be given more serious consideration in the totality of the problem than has been accorded them up to now.

Hammond's prospective study,[13] on the other hand, exhibited a tendency for CHD death rates to increase with degree of inhalation. The data might have been more illuminating, however, if the noninhalers had not been lumped together with those who inhaled slightly. Again we find that Hammond's subjects who did not inhale or inhaled slightly had much higher death rates than the nonsmokers.

Ex-Smokers.—The 1964 report points out that, "men who stop smoking have a lower death rate from coronary disease than those who continue," and cites the six-year experience of the combined Albany and Framingham study[7] and Hammond and Horn's[11] 44 months follow-up of more than 187,000 American men.

The studies since have added considerably more material, but the nature of the results can hardly be said to clarify the subject. Thus, while Doll and Hill's study of British doctors,[8] Dorn's study of US veterans,[10] the Hammond study of American men,[13] and the study of Canadian veterans[12] give lower CHD rates for ex-smokers than of those currently smoking cigarettes, higher CHD rates are found among ex-smokers than among those currently smoking cigarettes and nonsmokers in the Tecumseh, Michigan study,[7] Reid and co-workers' study of migrants,[14] and the national health survey.[15] The combined Albany and Framingham study[16] shows former cigarette smokers with a lower CHD death risk than nonsmokers, and about the same level of CHD risk for fatal and nonfatal myocardial infarction as between former cigarette smokers and nonsmokers. The authors state, "The risk of CHD or death for ex-cigarette smokers in these two populations (Albany and Framingham) was nearly equal to the risk for those who never smoked . . ."

The mortality ratios of ex-cigarette smokers found in Dorn's data recede to an intermediate position between the corresponding figures for current smokers and nonsmokers, and that former cigar and pipe smokers have higher mortality ratios than those who continue smoking (as Dorn had reported earlier)." Dorn had suggested that many smokers may have stopped smoking because of ill health, but did not understand why this should be true for cigar and pipe smokers but not for cigarette smokers. For this reason, Kahn excluded from his calculations those individuals who had stopped smoking because of doctors' orders, but the effect persisted among cigar and pipe smokers just the same. Kahn does not find "obvious" why this effect persists. Some complications were also apparent in the Hammond study.[13] Ex-cigarette smokers who quit recently (less than one year ago for those who formerly smoked 1 to 19 cigarettes a day and less than five years ago for those persons who smoked 20 or more cigarettes a day) had CHD death rates as high as or higher than persons currently smoking cigarettes. This seemingly anomalous finding was further investigated in another study by Hammond and Garfinkel[17] in which ill health was suggested as a complicating factor in stopping smoking or reducing cigarette consumption. They reported that the bias introduced by the influence of ill health on smoking habits "makes it difficult to evaluate the degree of benefit derived from giving up smoking, and even more difficult to determine whether giving up the habit results in a reduction of death rates soon after."

Further conflicting results are to be found with respect to the first years after smoking is stopped and the long-term cessation of smoking. A sharp fall in CHD mortality is seen in the Doll and Hill study[8] in the first five years after the subjects stopped smoking (followed by a rise in the next period), but only moderate declines are to be found in the early years following discontinuance of smoking in Dorn's US veterans[10] and Hammond's American men.[13] The CHD rates of ex-smokers, after the longest period of cessation of cigarette smoking, fall to a level *below* that of persons currently smoking cigarettes but still *higher* than nonsmokers in the Doll and Hill,[8] Dorn,[10] and Canadian veterans studies,[12] and in the Hammond survey of the category of persons who smoked 20 or more cigarettes a day.[13] In the Hammond study, the CHD death rate dropped to the level of nonsmokers for the persons who smoked 1 to 19 cigarettes a day.

The extreme difficulties, in these kinds of studies, of clearly unraveling the effect of discontinuance of cigarette smoking on CHD rates is recognized by Doll and Hill,[8] Kahn,[11] Hammond and Garfinkel,[17] Epstein et al,[7] Reid et al,[14] K[illegible][18] and others. Doll and Hill, who gave much attention to this subject, pointed out, for example, that much of the fall of mortality with discontinuance of smoking ". . . may be an artifact, due merely to the selective failure of doctors to give up smoking when they are already ill."[8] Epstein et al, in explanation of their higher CHD rates of ex-smokers relative to both current smokers and nonsmokers, have said that their finding ". . . is to be expected, since persons with disease are more likely to discontinue the habit."[7] They all make the point that

1005050664

Source: https://www.industrydocuments.ucsf.edu/docs/ntlk0000

1968 Page 382 (g)

the bias introduced by ill health on smoking habits "dirties up" the data of ex-smokers and makes it therefore difficult to establish clear-cut trends and effects.

Summary

With this presentation of the additional information since the Surgeon General's 1964 report on the subject of smoking and coronary heart disease (considering the epidemiological studies only), we are now able to assess the nature of the evidence which has led to the extension and magnification of the claims of the effect cigarette smoking has on mortality and disability from CHD made by numerous people.

The conclusion of the Surgeon General's 1964 Report that male cigarette smokers have a higher death rate from CHD than men who do not smoke has been confirmed in the new studies published since the report was issued. This conclusion must be accepted as an established observation. But the question still remains as to the interpretation to be given to this statistical observation. The most such an epidemiological observation " . . . can do is to demonstrate the existence of a relationship between cigarette smoking and various health characteristics; it cannot establish any existing relationship as a causal one,"[5] and ". . . inferences on causality cannot depend on the demonstration of association alone."[6] The first phase of the epidemiological approach to a disease problem is the determination of the statistical association; the second phase is the derivation of biological inferences from the pattern of statistical association."

What inferences, then, may be drawn from the additional epidemiological evidence which has appeared since the 1964 report? And particularly, since the 1964 report concluded ". . . but it is not clear that the association has causal significance," what new inferences may be drawn with respect to causality?

Our survey of the new epidemiological evidence has indicated that, for all practical purposes, pipe or cigar smoking is not associated with excess deaths and disabilities due to coronary heart disease (CHD), leaving cigarette smoking as the focus of necessary attention. The weight of evidence, at the moment, is that angina pectoris as the sole or initial manifestation of CHD is probably unrelated to cigarette smoking. There are still some lingering questions with regard to the prevalence data in this regard, but conclusions drawn from prevalence data are generally considered less reliable than incidence rates. This would leave myocardial infarction (and sudden deaths) as the principal conditions statistically associated with cigarette smokers. In this connection, Doll and Hill have pointed out that a relationship with smoking is characteristic of only a little more than one-half the total number of deaths attributed to coronary thrombosis.[7] This erosion of postulated CHD smoking risks is further enhanced by the Framingham heart study which suggested that the effects of smoking is limited to those persons with "already compromised circulations."

With respect to amount of cigarette smoking, the new data do not confirm the finding of the Surgeon General's report of a consistent rising gradient of CHD mortality with increased amounts of cigarettes smoked, but on the contrary give a complex and hardly consistent picture showing a profusion of inconsistencies and inversions. The new data have in effect raised serious questions as to the validity of the 1964 report on this point. Duration of cigarette smoking has been found to be unassociated with excess CHD mortality in cigarette smokers in the new data, and conflicting results are obtained with regard to the effect of inhalation. Finally, the new data dealing with the effect of discontinuance of cigarette smoking (a subject considered of such great significance in lung cancer mortality) frequently give contradictory and inconsistent findings, and pose a virtually insoluble problem as to valid interpretations and conclusions that may be drawn from such data in the present study designs. The bias introduced by the influence of ill health on smoking habits makes it extremely difficult to determine whether giving up the habit actually results in a reduction of death rates soon after. Accordingly, in some respects the epidemiological evidence is less clear now than at the time of the 1964 report.

It is, therefore, difficult to see from the new epidemiological data how valid causal inferences can be drawn that *cigarette smoking* is linked to excess CHD deaths or that the excess CHD deaths are "*caused by*" cigarette smoking. We do not know whether or not there is a causal connection between cigarette smoking and increased deaths from coronary heart disease.

The present state of our knowledge still suggests (as the Surgeon General's Advisory Committee's Report on Smoking and Health stated in 1964) that "male cigarette smokers have a higher death rate from coronary artery disease than nonsmoking males, but it is not clear that the association has causal significance."

This investigation was supported in part by the Fund for Research and Teaching of the Department of Nutrition, Harvard University School of Public Health, Boston.

References

1. *Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service.* US Dept of Health, Education and Welfare, 1964.

2. Hearings before the Subcommittee on Tobacco of the Committee on Agriculture, House of Representatives, series 2, p 5, Jan 27, 1964.

3. Hearings before the Committee on Commerce, US Senate, part 1, serial 89-5, March 22, 1965.

4. Stamler, J.: "Nutrition, Metabolism and Atherosclerosis," in Ingelfinger, F.J.; Relman, A.S., and Finland, M. (eds.): *Controversy in Internal Medicine*, Philadelphia: W.B. Saunders Co., 1966, pp 27-59.

5. Hirn, D.: An Analysis of the Educational Problems of Controlling Cigarette Smoking, read before the International Cancer Congress, Tokyo, Oct 26, 1966.

6. The Health Consequences of Smoking, Public Health Service publication 1696, 1967.

10050665

Source: https://www.industrydocuments.ucsf.edu/docs/ntlk0000

7. Doll, R., and Hill, A.B.: Mortality in Relation to Smoking: Ten Years Observations of British Doctors (Part I), *Brit Med J* 1:1399-1410 (May 30) 1964.

8. Doll, R., and Hill, A.B.: Mortality in Relation to Smoking: Ten Years' Observations of British Doctors (Concluded), *Brit Med J* 1:1460-1467 (June 6) 1964.

9. Doll, R., and Hill, A.B.: "Mortality of British Doctors in Relation to Smoking: Observations on Coronary Thrombosis," in Haenszel, W. (ed.): Epidemiological Approaches to the Study of Cancer and Other Diseases, *Nat Cancer Inst Monog*, No. 19, pp 205-268 (Jan) 1966.

10. Doyle, J.T., et al: The Relationship of Cigarette Smoking to Coronary Heart Disease: The Second Report of the Combined Experience of the Albany, NY, and Framingham, Mass, Studies, *JAMA* 190:886-890 (Dec 7) 1964.

11. Kahn, H.A.: "The Dorn Study of Smoking and Mortality Among U.S. Veterans: Report on 8½ Years of Observation," in Haenszel, W. (ed.): Epidemiological Approaches to the study of Cancer and Other Diseases, *Nat Cancer Inst Monog*, No. 19, pp 1-125 (Jan) 1966.

12. Hammond, E.C.: "Smoking in Relation to the Death Rates of 1 Million Men and Women," in Haenszel, W. (ed.): Epidemiological Approaches to the Study of Cancer and Other Diseases, *Nat Cancer Inst Monog*, No. 19, pp 127-204 (Jan) 1966.

13. Best, E.W.R., et al: Summary of a Canadian Study of Smoking and Health, *Canad Med Assoc J* 96:1164-1168 (April 15) 1967.

14. McDonough, J.R., et al: Coronary Disease Among Negroes and Whites in Evans County, Georgia, *J Chronic Dis* 18:443-468 (March) 1965.

15. Epstein, F.H., et al: Epidemiological Studies of Cardiovascular Disease in a Total Community—Tecumseh, Michigan, *Ann Intern Med* 62:1170-1184 (June) 1965.

16. Reid, D.D., et al: "Studies of Disease Among Migrants and Native Populations in Great Britain, Norway, and the United States: III. Prevalence of Cardiorespiratory Symptoms Among Migrants and Native-Born in the United States," in Haenszel, W. (ed.): Epidemiological Approaches to the Study of Cancer and Other Diseases, *Nat Cancer Inst Monog*, No. 19, pp 321-346 (Jan) 1966.

17. Shapiro, S., et al: The H.I.P. Study of Incidence and Prognosis of Coronary Heart Disease, *J Chronic Dis* 18:527-553 (June) 1965.

18. Frank, C.W., et al: Myocardial Infarction in Men: Role of Physical Activity and Smoking in Incidence and Mortality, *JAMA* 198:1241-1245 (Dec 19) 1966.

19. Frank, C.W., et al: Physical Inactivity as a Lethal Factor in Myocardial Infarction Among Men, *Circulation* 24:1022-10[illegible] (Dec) 1961.

20. *Cigarette Smoking and Health Characteristics: United States—July 1964-June 1965*, series 10, No. 34, National Center for Health Statistics, US Dept of Health, Education and Welfare, Public Health Service, May 1967.

21. Freidman, G.D., et al: Comparison of Prevalence, C[illegible] History and Incidence Data in Assessing the Potency of Risk Factors in Coronary Heart Disease, *Amer J Epidem* 83:566-[illegible] (March) 1966.

22. Cederlof, R., et al: Morbidity Among Monozygotic Twins, *Arch Environ Health* 10:346-350 (Feb) 1965.

23. Kannel, W.B.; Dawber, T.R.; and McNamara, P.M.: Detection of the Coronary-Prone Adult: The Framingham Study, *J Iowa Med Soc* 51:533-534 (Jan) 1966.

24. National Center for Health Statistics: *Mortality From Diseases Associated With Smoking: United States 1950-64*, Vital and Health Statistics, series 20, No. 4, Public Health Service publication 1000, October 1966.

25. Seltzer, C.C.: Morphologic Constitution and Smoking, *JAMA* 183:639-645 (Feb 23) 1963.

26. Doyle, J.T., et al: Cigarette Smoking and Coronary Heart Disease: Combined Experience of the Albany and Framingham Studies, *New Eng J Med* 266:796-801 (April 19) 1962.

27. Hammond, E.C., and Horn, D.: Smoking and Death Rates—Report of 44 Months of Follow-up of 187,783 Men: I. Total Mortality; II. Death Rates by Cause, *JAMA* 166:1159-1172 (March 8); 1294-1308 (March 15) 1958.

28. Hammond, E.C., and Garfinkel, L.: "The Influence of Health on Smoking Habits," in Haenszel, W. (ed.): Epidemiological Approaches to the Study of Cancer and Other Diseases, *Nat Cancer Inst Monog*, No. 19, pp 239-285 (Jan) 1966.

29. Keys, A.: Diet and Coronary Heart Disease Throughout the World, *Cardiol Pract* 13:225-244 (Feb) 1962.

30. Epstein, F.H.: The Epidemiology of Coronary Heart Disease, *J Chronic Dis* 18:735-774 (Aug) 1965.

31. Lilienfeld, A.M.: "Epidemiological Concepts Applied to Studies of Chronic Diseases," in *Genetics and the Epidemiology of Chronic Diseases*, US Dept of Health, Education and Welfare, Public Health Service publication 1,163, pp 87-102, February 1965.

1005050666

Source: https://www.industrydocuments.ucsf.edu/docs/ntlk0000